IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	De Sauvage et al.
Appl. No.	:	08/793,653
Filed	:	February 27, 1997
For	:	OB PROTEIN IMMUNOGLOBULIN CHIMERAS
Examiner	:	Zachary C. Howard

Group Art Unit 1646

I hereby certify that this correspondence and all marked attachments are being deposited with the United States Postal Service as first-class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA, 22313, on

June 23, 2006
(Date)

Eli A. Loots, Reg. No. 54,715

REQUEST FOR CORRECTED FILING RECEIPT

Commissioner for Patents
P.O. Box 1450
Office of Initial Patent Examination
Customer Service Center
Alexandria, VA 22313-1450

Dear Sir:

Applicants hereby request that the Official Filing Receipt, a copy of which is enclosed, be corrected to reflect the complete priority information, as indicated on the previously submitted Request for Corrected Filing Receipt dated January 14, 2002 (copy enclosed) and in the Amendments to the Specification submitted November 22, 2005 (copy enclosed). The correct priority information is as follows:

> This Application is a §371 national phase of PCT/US96/20718, 12/19/96.
> PCT/US96/20718 claims priority to and is a continuation of US 08/667184, 06/20/96.
> PCT/US96/20718 claims priority to US Provisional Appl. No. 60/040911, 12/27/95.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 6/23/06

By: _____

Eli A. Loots
Registration No. 54,715
Attorney of Record
Customer No. 20,995
(415) 954-4114

PTO-103X
(Rev. 8-95)

FILING RECEIPT

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

GD/LS

APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTORNEY DOCKET NO.	DRWGS	TOT CL	IND CL
08/793,653	02/27/97	1801	$1,064.00	P0985P2	27	27	3

RECEIVED
FEB 23 1998
GENENTECH, INC.
LEGAL DEPT.

GINGER R. DREGER
GENENTECH, INC.
460 POINT SAN BRUNO BLVD.
SOUTH SAN FRANCISCO CA 94080-4990

Receipt is acknowledged of this nonprovisional Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please write to the Application Processing Division's Customer Correction Branch within 10 days of receipt. Please provide a copy of the Filing Receipt with the changes noted thereon.

Applicant(s)

FREDERIC DE SAUVAGE, FOSTER CITY, CA; NANCY LEVIN, NEWBURY PARK, CA; RICHARD L. VANDLEN, HILLSBOROUGH, CA.

CONTINUING DATA AS CLAIMED BY APPLICANT-
THIS APPLN IS A 371 OF PCT/US96/20718 12/19/96
PCT/US96/20718 CLAIMS PRIORITY TO AND IS ACON OF US 08/667184 6/20/96
and US 60/040911 12/27/95

FOREIGN FILING LICENSE GRANTED 02/13/98

TITLE
OB PROTEIN DERIVATIVES HAVING PROLONGED HALF-LIFE

PRELIMINARY CLASS: 435

(see reverse)

LICENSE FOR FOREIGN FILING UNDER
Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "FOREIGN FILING LICENSE GRANTED" followed by a date appears on the reverse side of this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.11. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related application(s) filed under 37 CFR 1.62 which meets the provisions of 37 CFR 5.15(a). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations, especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR Parts 121-128)); the Office of Export Administration, Department of Commerce (15 CFR 370.10 (j)); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "FOREIGN FILING LICENSE GRANTED" DOES NOT appear on the reverse side of this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

1646

Docket No.: GENENT.052CP2

June 23, 2006
Page 1 of 1

Please Direct All Correspondence to Customer Number **20995**

TRANSMITTAL LETTER

REQUEST FOR CORRECTED FILING RECEIPT

Applicant	:	De Sauvage et al.
App. No	:	08/793,653
Filed	:	February 27, 1997
For	:	OB PROTEIN IMMUNOGLOBULIN CHIMERAS
Examiner	:	Zachary C. Howard
Art Unit	:	1646

CERTIFICATE OF MAILING

I hereby certify that this correspondence and all marked attachments are being deposited with the United States Postal Service as first-class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on

June 23, 2006
(Date)

Eli A. Loots, Reg. No. 54,715

Office of Initial Patent Examination
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Enclosed for filing in the above-identified application are:

(X) A Request for Corrected Filing Receipt

(X) A copy of the Filing Receipt with corrections marked.

(X) A copy of previous Request for Corrected Filing Receipt submitted January 14, 2002.

(X) A copy of the Amendment and Response to Office Action submitted November 22, 2005.

(X) Return prepaid postcard.

Eli A. Loots
Registration No. 54,715
Attorney of Record
Customer No. 20,995
(415) 954-4114

2707537
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COPY

PATENT

Case Docket No. GENENT.052CP2
Date: January 14, 2002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	DeSauvage et al.
Appl. No.	:	08/793,653
Filed	:	February 27, 1997
For	:	OB PROTEIN-IMMUNOGLOBULIN CHIMERAS
Examiner	:	G. Draper
Group Art Unit	:	1646

I hereby certify that this correspondence and all marked attachments are being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231, on

January 14, 2002
(Date)

Ginger R. Dreger, Reg. No. 33,055

TRANSMITTAL LETTER

COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

Dear Sir:

Enclosed for filing in the above-identified application are:

(X) A Request for Corrected Filing Receipt.

(X) Copies of the Filing Receipt, Amendment and Petition.

(X) The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Account No. 11-1410.

(X) Return prepaid postcard.

Ginger R. Dreger
Registration No. 33,055
Attorney of Record

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GENENT.052CP2

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	De Sauvage et al.	Group Art Unit: 1646
Appl. No.	:	08/793,653	
Filed	:	February 27, 1997	
For	:	OB PROTEIN-IMMUNOGLOBULIN CHIMERAS	
Examiner	:	G. Draper	

REQUEST FOR CORRECTED FILING RECEIPT

Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Applicants hereby request that the Official Filing Receipt, a copy of which is enclosed, be corrected to reflect the correct and complete priority data as claimed by Applicants. Presently, the Domestic Priority data is incomplete. Please replace the priority data as follows.

This application is a 371 of PCT/US96/20718 filed on December 19, 1996, and claims priority to U.S. Application Serial No. 08/667,184, filed on June 20, 1996, now abandoned, and to U.S. Provisional Application Serial No. 60/040,911, filed on December 27, 1995.

Please note that the title of the application was changed to OB PROTEIN-IMMUNOGLOBULIN CHIMERAS by an Amendment filed on November 25, 1998.

Further, please note that a Petition was filed on November 25, 1998, requesting the deletion of Nancy Levin as an inventor. However, Applicants have not received any indication that their petition has been accepted.

Copies of the Amendment and Petition are enclosed.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: January 14, 2002

By: _____

Ginger R. Dreger
Registration No. 33,055
Attorney of Record
620 Newport Center Drive
Sixteenth Floor
Newport Beach, CA 92660
(415) 954-4114

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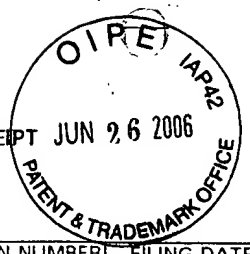
PTO-103X
(Rev. 8-95)



FILING RECEIPT JUN 26 2006

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
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OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

GD/L

APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTORNEY DOCKET NO.	DRWGS	TOT CL	IND CL
08/793,653	02/27/97	1801	$1,064.00	P0985P2	27	27	3

GINGER R. DREGER
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460 POINT SAN BRUNO BLVD.
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Receipt is acknowledged of this nonprovisional Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please write to the Application Processing Division's Customer Correction Branch within 10 days of receipt. Please provide a copy of the Filing Receipt with the changes noted thereon.

Applicant(s)

FREDERIC DE SAUVAGE, FOSTER CITY, CA; NANCY LEVIN, NEWBURY PARK, CA; RICHARD L. VANDLEN, HILLSBOROUGH, CA.

CONTINUING DATA AS CLAIMED BY APPLICANT-
THIS APPLN IS A 371 OF PCT/US96/20718 12/19/96

FOREIGN FILING LICENSE GRANTED 02/13/98
TITLE
OB PROTEIN DERIVATIVES HAVING PROLONGED HALF-LIFE

PRELIMINARY CLASS: 435

(see reverse)

Patent Docket P0985P2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of FREDERIC DE SAUVAGE et al. Serial No.: 08/793,653 Filed: 27 FEBRUARY 1997 For: OB PROTEIN DERIVATIVES	Group Art Unit: 1646 Examiner: DRAPER, G. **CERTIFICATE OF MAILING** I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, D.C. 20231 on November 25, 1998 Aida A. Miclat

PETITION, STATEMENT AND FEE DELETING CORRECTLY NAMED ORIGINAL INVENTORS WHO ARE NOT INVENTORS OF INVENTION NOW BEING CLAIMED UNDER 37 C.F.R. 1.48(b)

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

The present Petition is filed to request the deletion of Nancy Levin as an inventor of the invention claimed in the above-identified patent application.

Nancy Levin was originally properly included as an inventor, however, due to the amendments of the original claims, as requested in the Amendment filed concurrently with the present Petition, her invention is no longer claimed in the present application.

The present Petition is diligently made. Commissioner is hereby authorized to charge Deposit Account No. 07-0630 in the amount of $130.00 to cover the fees for this Petition required as set forth in 37 CFR 1.17(h), and to charge the deposit account for any further fees in regard to this patent application. **A duplicate copy of this Petition is enclosed for this purpose.**

Respectfully submitted,
GENENTECH, INC.

By: _____
Ginger R. Dreger
Reg. No. 33,055

Date: November 25, 1998
1 DNA Way
South San Francisco, CA 94080-4990
Tel: (650) 225-3216
Fax: (650) 952-9881

Patent Docket P0985P2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of FREDERIC DE SAUVAGE et al. Serial No.: 08/793,653 Filed: 27 FEBRUARY 1997 For: OB PROTEIN DERIVATIVES	Group Art Unit: 1646 Examiner: DRAPER, G. CERTIFICATE OF MAILING I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, D.C. 20231 on November 25, 1998 Aida A Miclat

AMENDMENT UNDER 37 C.F.R. §1.111

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

This is in response to the Office Action mailed on May 27, 1998 (Paper No. 3) setting a three months term. A request for a three months extension of time accompanies the present Amendment, setting the new term to November 27, 1998.

Kindly amend this application in the following aspects.

In the Specification:

On page 1, please cancel the title of the present application, and replace it with --OB protein-immunoglobulin chimeras--.

In the Claims:

Please cancel claims 1-12, and 27, without prejudice. Applicants specifically preserve the right to pursue the currently canceled claims in one or more continuing applications.

Please amend claim 13 as follows:

13. (Amended) A chimeric polypeptide comprising [an OB protein] the amino acid sequence [capable of binding to a native OB receptor] of a native OB protein, with or without the initiating N-terminal methionine and with or without the native signal sequence, [linked] fused to an immunoglobulin heavy chain constant domain sequence.

Please amend claim 14 as follows:

14. (Amended) A chimeric polypeptide of claim 13 wherein said immunoglobulin constant domain sequence [is a constant domain sequence] comprises the hinge, CH2 and CH3 regions of an IgG.

Please amend claim 18 as follows:

18. (Amended) An isolated nucleic acid [sequence] molecule encoding [an OB protein-immunoglobulinfusion] a chimeric polypeptide comprising the amino acid sequence of a native OB protein, with or without the initiating N-terminal methionine and with or without the native signal sequence, fused to an immunoglobulin heavy chain constant domain sequence.

Please amend claim 21 as follows:

21. (Amended) A process comprising culturing the host cells of claim [16] 20 so as to express the nucleic acid encoding [an OB protein-immunoglobulin fusion] said chimeric polypeptide, and recovering said chimeric polypeptide.

Please amend claim 22 as follows:

22. (Amended) The process of claim 21 wherein said host cells are cotransformed with nucleic acid encoding at least two OB protein-immunoglobulin heavy chain constant domain fusions.

In claim 25, line 1, cancel "claim 20" and replace it with --claim 24--.

Please add the following new claim:

--28. The nucleic acid of claim 18 encoding a chimeric polypeptide comprising a mature native human OB polypeptide fused, at its C-terminus, to the N-terminus of an IgG constant domain sequence comprising the hinge, CH2 and CH3 regions.--

I.

Support for the Amendments

The foregoing amendments in the claims are supported at least in the paragraph bridging pages 4 and 5, and at page 9, lines 8-27. The amendments do not introduce new matter into the specification, therefore, their entry is respectfully requested.

II.

Formal Matters

Applicants were requested to make the title of the invention more descriptive. The foregoing amendment is believed to address this request.

Applicants were requested to correct the dependencies on claims 25 and 21, respectively. The foregoing amendments in the specification include these corrections.

III.

Double Patenting Rejections

Claims 1-27 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 13-23, 26, and 28-41 of copending application Serial No. 08/667,184. It is applicants intention to abandon copending application Serial No. 08/667,184 by failing to file a response to the pending Office Action mailed on April 29, 1998, and pursue the overlapping subject matter in the present application. Accordingly, the withdrawal of the present rejection is respectfully requested.

IV.

Objections and Rejections under 35 U.S.C. §112

Claims 7-9 were objected to as being "substantial duplicates" of claim 1. Without acquiescence in the Examiner's position, claims 7-9 have been canceled which moots their rejection.

Claim 21 was rejected under 35 U.S.C. §112, second paragraph, as being "indefinite." According to the rejection, this claim is "incomplete for failing to recite a recovery step", which ensures that the desired chimera is prepared. Claim 21 has been amended to include a recovery step, which should obviate the present rejection.

Claims 1-27 were rejected under 35 U.S.C. §112, first paragraph, "because the specification, while being enabling for the nature form of the Ob protein and certain limited derivatives fused to Ig or PEG, does not reasonably provide enablement" for all long-half derivatives covered by these claims. Without acquiescence in this rejection, claims 1-12 and 27 have been canceled, and the remaining claims have been amended to cover chimeric polypeptides comprising native OB proteins, with or without the N-terminal initiating methionine and with or without the native signal sequence. As the Examiner has

acknowledged that the specification provides sufficient enablement for this subject matter, the withdrawal of the present rejection is respectfully requested.

Claims 1-3, 7-12 and 27 were rejected as being generic to a long half-life derivative of the OB protein, without reciting the make-up of the product. The cancellation of these claims, which was done without prejudice and without acquiescence in the Examiner's position, moots this rejection.

Claims 1-27 were rejected as non-enabled "for the full scope of the Ob protein that can be derivatized in order to have a product with the improved half-life." The Examiner acknowledged that applicants have shown that "the mature form of the Ob protein can be fused to the Ig or PEG and still maintain the activity of the protein", but found these results insufficient "to be reasonably predictive of the use of any Ob protein that will bind to the cognate receptor." As the claims have been amended to cover Ig fusions of certain well specified native OB proteins and derivatives, the present rejection is believed to be moot.

V.

Rejections Over Prior Art

Claims 1-3, 5-12 and 27 were rejected under 35 U.S.C. §103(a) as "being unpatentable over any one of Zhang et al., DiMarchi et al. or Basinski et al. in view of any one of Hakimi et al. ('356), Greenwalt et al. ('924), Haratani ('546), Nishimura et al. ('316), Davis et al. ('337), Yamasaki et al. (1988 or 1990) or Francis." The primary references were cited for their disclosure of mutant forms of the Ob polypeptide along with suggestions that such forms can be used to treat weight disorders. The secondary references were cited for their disclosure of making PEG conjugates of various polypeptides, not including OB proteins, to enhance their bioavailability. The Examiner concluded that "the skilled artisan would have been motivated by the combined teachings of both the primary and secondary reference for conjugating the Ob mutant of the primary to the various polymers of the secondary reference, and would

reasonably expected that such conjugation would have provided an additional benefit form use therapeutically."

As the claims rejected on this ground have been cancelled, the rejection is moot. It is emphasized, however, that the cancellation was done without acquiescence in the Examiner's position, and without prejudice. Applicants specifically retain the right to pursue the subject matter of the cancelled claims in one or more continuing applications.

Claims 1-3, and 7-27 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Zhang et al., Basinski et al. ('744 or '886), DiMarchi et al. ('954 or '336), in view of Shin et al. or Ashkenazi et al. The primary references were cited for their disclosure of human and murine Ob proteins and their mutant forms. The secondary references were relied upon for their disclosure of chimeric proteins including fusions of various mature proteins or polypeptides to immunoglobulins or their single chains, and of the advantages of such fusions. Neither the primary nor the secondary references disclose OB protein - Ig fusions. The Examiner represents, however, that such fusion proteins are prima facie obvious since they can be readily made by using the OB proteins taught in the primary reference in the fusions disclosed by the secondary references. In addition, the Examiner noted that prima facie obviousness is further supported by the teachings of the primary references for the potential benefits of using such protein, and also because of the broad and generic teaching of the secondary references that the disclosed conjugates can be made with different proteins.

Applicants vigorously traverse this rejection.

Applicants concede that native OB proteins were known in the art at the priority date of the present application. Similarly, it was known (as the secondary references attest) how to make receptor-immunoglobulinfusions (immunoadhesins), which were known to be useful, for example in therapy or as diagnostics. Indeed, the relevant art is clearly acknowledged in the Background Art section, and at pages 8-9 of the present application.

The specific OB protein-immunoglobulinchimeras of the present invention are believed to be patentable over the cited combination of references in view of their unexpected properties.

At the priority date of the present application, the receptor or receptors of the OB protein were unidentified. Researchers suggested, however, that at least one OB receptor, which was thought to be the biologically significant one, is localized in the brain.

Coleman, Diabetologica 14, 141-148 (1978) hypothesized that the ob receptor is encoded at the *db* locus of the hypothalamus. Campfield et al., Science 269, 546-49 (1995) reported experimental evidence that mouse OB protein can alter feeding behavior and energy balance when placed directly in the lateral ventricle of the brain of obese *ob/ob* and lean mice. The authors interpreted this finding to suggest that "one or more brain areas are among the target sites for mouse OB protein." They further suggested that the "identification of these brain areas will facilitate studies aimed at elucidating the neuronal pathways and networks and the underlying molecular mechanisms by which OB protein can influence feedings behavior and energy balance." (Page 548, concluding sentence.) Although the existence of peripheral receptors was not entirely ruled out, Maffei et al., Proc. Natl. Acad. Sci. 92, 6957-60 (1995) found that the expression of the ob gene in adipose tissue of mice with hypothalamic lesions did not result in a lean phenotype. They noted that the "most parsimonious explanation" of their data is that "the ob protein functions as an endocrine signaling molecule that is secreted by adipocytes and acts, directly or indirectly, on the hypothalamus." The authors added that "[d]irect effects on the hypothalamus would require that mechanisms exist to allow passage of the ob gene product across the blood-brain barrier. Mechanisms involving the circumventricular organ and/or specific transporters could permit brain access of a molecule the size of that encoded by the ob gene." (Page 6050, second column.)

The present inventors have found that chimeric polypeptides in which the OB protein is fused to an immunoglobulin constant domain sequence are effective in reducing body weight and adipose tissue depots. The present inventors have additionally found that such chimeric

polypeptides were significantly more potent than native human OB. These findings have been entirely unexpected against the background of the referenced prior art which suggested that the biologically relevant OB receptor is located in the brain. In view of their large molecular weight, the OB protein - Ig chimeras would not have been expected to be able to cross the blood-brain barrier, and therefore would have been expected biologically inactive. Hence, the finding of the present inventors that such chimeras are not only biologically active but more potent than the OB protein alone was entirely unexpected and is deserving patent protection.

In view of the foregoing arguments, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

The present Amendment is accompanied by a Petition under 37 C.F.R. §1.48(b) requesting the deletion of Nancy Levin as an inventor. Dr. Levin was originally properly included as inventor, but due to claim amendments, her invention is no longer claimed in the present application.

The present application is now believed in prima facie condition for allowance, and an early action to that effect is respectfully solicited.

Respectfully submitted,
GENENTECH, INC.

Date: November 25, 1998

By: _____
Ginger R. Dreger
Reg. No. 33,055

1 DNA Way
So. San Francisco, CA 94080-4990
Phone: (650) 225-3216
Fax: (650) 952-9881

COPY

GENENT.052CP2

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	De Sauvage et al.
Appl. No.	:	08/793,653
Filed	:	February 27, 1997
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11/22/05

(Date)

Eli A. Loots, Reg. No. 54,715

AMENDMENT AND RESPONSE TO OFFICE ACTION

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the Office Action mailed from the United States Patent and Trademark Office on July 29, 2005, consideration of the following remarks and Amendment are respectfully requested. Additionally, Applicants request a one-month extension of time.

Amendments to the Specification are on page 2 of this paper.

Amendment to the Claims begins on page 3 of this paper.

Interview Summary begins on page 4 of this paper

Remarks/Arguments begin on page 5 of this paper.

AMENDMENTS TO THE SPECIFICATION

Please add the following paragraph to page 1, after the Title of the Invention:

This application is a §371 national phase application of PCT/US96/20718, filed December 19, 1996, which claims priority to and is a continuation of U.S. Application Serial Number 08/667,184, filed on June 20, 1996, now abandoned, and to U.S. Provisional Application No: 60/040,911, filed on December 27, 1995.

AMENDMENTS TO THE CLAIMS

1.-23. **(Cancelled)**

24. **(Currently Amended)** A method of treating bulimia ~~associated with the abnormal expression or function of the OB gene or for eliciting a biological response mediated by an OB receptor~~ comprising, administering to a patient having bulimia a therapeutically effective amount of **[[the]]** a chimeric polypeptide, wherein said chimeric polypeptide comprises the amino acid sequence of a native OB protein, with or without the initiating N-terminal methionine and with or without the native signal sequence, fused to an immunoglobulin heavy chain constant domain sequence.

25.-28 **(Cancelled)**.

29. **(Currently amended)** The method of Claim 24, wherein the administration of the chimeric polypeptide results in ~~biological response mediated by an OB receptor is~~ a decrease in food intake.

30. **(Currently amended)** The method of Claim 24, wherein the administration of the chimeric polypeptide results in ~~biological response mediated by an OB receptor is~~ an increase in energy use.

31. **(New)** The method of Claim 24, wherein the therapeutically effective amount is between 1 micrograms/kg to 100 mg/kg per day.

32. **(New)** The method of Claim 24, wherein the chimeric polypeptide further comprises two OB polypeptide IgG heavy chain fusions linked to each other by at least one disulfide bond to yield a homodimeric immunoglobulin-like structure.

33. **(New)** The method of Claim 24, wherein the chimeric polypeptide further comprises at least one of said OB polypeptide-IgG heavy chain fusions associated with an immunoglobulin light chain.

34. **(New)** The method of Claim 24, wherein the chimeric polypeptide further comprises the hinge, CH2, and CH3 domains of IgG-1.

35. **(New)** The method of Claim 24, wherein the chimeric polypeptide comprises at least the sequence of amino acids 1-167 of the full length OB protein (amino acids 1-167 of SEQ ID NO: 2).

36. **(New)** The method of Claim 24, wherein the chimeric polypeptide comprises at least SEQ ID NO: 2.

INTERVIEW SUMMARY

Applicants thank Examiners Howard and Bunner for the helpful telephonic interview conducted on October 5, 2005 with Applicant's representative, Eli Loots. In the interview, the rejection of the claims under 35 U.S.C. §112 was discussed. It was noted that the rejection was a scope of enablement rejection which primarily focused on the breadth of the phrase "treating a condition associated with...." Additionally, it was suggested that the existence of references which suggest or support a link between bulimia would be relevant for rebutting the assertions in the rejection. Additionally, references, which suggest that resistance to a compound does not mean immunity to the compound, would also be relevant in the consideration of the rejection. Finally, it was suggested that an amendment to Claim 24 to further clarify "abnormal expression or function" could help resolve the above issues.

REMARKS

Claims 14, 16-26, and 28-30 were previously pending. These claims were rejected in the Office Action dated July 29, 2005. Claims 14, 15-23, and 25-28 have been cancelled. Applicants reserve the right to pursue the subject matter of the cancelled claims at a later time. New Claims 31-36, all of which depend from Claim 24, have been added. Thus, Claims 24, 29, and 30-36 are currently pending. Claim 24 has been amended to provide proper antecedent basis for the phrase "chimeric polypeptide." Claim 24 has also been amended to explicitly define some of the conditions and to remove the reference to the term "biological response." Support for the amendment can be found in the specification and claims, for example, Claims 24 and 25 and page 17 of the specification. Claims 29 and 30 have been amended in light of the amendments to Claim 24. Support for these amendments can be found in the original claims and the specification. Support for the new claims can be found throughout the original specification and claims. For example, support can be found on page 18, second full paragraph and last paragraph, Claims 16 and 17, SEQ ID NO: 2, and Figure 6. No new matter has been added by these amendments.

Applicants request the insertion of the above particular priority paragraph into the specification. Applicants note that a request for a corrected filing receipt, noting the above information and requesting correction of the previous filing receipt in line with the above information, was filed January 12, 2002. However, Applicants have not had a response regarding this request yet. Applicants note that the above priority information was previously provided to the Patent Office and that it was acknowledged by the Patent Office in the Notification of Acceptance of Application Under 35 U.S.C. 371, mailed 12/04/97. Additionally, Applicants note that a Petition was filed on November 25, 1998 requesting the deletion of Nancy Levin as an inventor; however, Applicants have not received any indication that their petition has been accepted.

Applicants appreciate the consideration of the previously submitted references and the withdrawal of the rejection of Claims 24-26 under 35 U.S.C. §112. Claim 26 has been cancelled.

Reconsideration of the pending rejections in view of the above amendments and following remarks is respectfully requested.

Rejection under 35 U.S.C. §112

Claims 24-26, 29, and 30 stand rejected under 35 U.S.C. §112, first paragraph, as failing to "provide enablement for 1) a method of treating a condition associated with the abnormal expression or function of the OB gene or for eliciting a biological response mediated by an OB receptor, or 2) a composition for the treatment of obesity." Of the rejected claims, only Claims 24, 29, and 30 are currently pending. The Office Action states that this is a scope of enablement rejection. The nature of this rejection was affirmed in the Examiner interview.

As discussed during the interview, a large amount of the scope of enablement rejection stemmed from the use of the terms "condition" and "biological response." Applicants have amended Claim 24 to remove these terms and to more specifically define the particular condition being treated. As such, Applicants submit that many of the issues regarding the rejection have been addressed. However, Applicants supply the following comments to further demonstrate that the claims are adequately enabled.

Applicants note that some of the statements in the Office Action are incorrect regarding the effectiveness of leptin on non-ob/ob mutant organisms. In the Office Action, it was asserted that the OB protein only works on ob/ob mutants. The Examiner referred to Gale et al. (Recent Advance in Nutritional Sciences, 134:295-8, 2004) as suggesting that administration of leptin to patients with elevated leptin levels may not always be effective due to leptin resistance. Furthermore, Bell-Anderson was asserted as noting that there was variation in amount of weight loss that resulted from the administration of leptin. Applicants note that neither of the cited references actually asserts that any amount of leptin cannot have some impact on weight loss or obesity. Rather, the references appear to suggest that not everyone will have all of their weight permanently reduced when leptin is administered at certain levels and in certain manners. Applicants note that one reason that the above references may have characterized the effects of leptin as such is that, as noted below, lower levels of leptin (or less efficient versions of leptin) are likely to have been used in the references discussed by Bell and Gale. Moreover, these references might also be referring to finding a "magic-bullet" type treatment, where a single dose of the protein results in permanent and large decreases in weight for all people. Applicants are not claiming such impressive results, and are merely asserting that the claimed method results in some weight loss, at some point, for some amount of time.

More importantly, the above interpretation of the cited references is directly rebutted by the information in the present application, which demonstrates that OB protein can work as desired, even when it is not in an ob/ob background. Applicants direct the Examiner to page 20, lines 29-33 and Figure 1 of the present application, which demonstrate the effectiveness of administering OB to lean (*i.e.*, non ob/ob) mice. Thus, it is clear from the specification itself that organisms without the ob/ob mutation, including lean subjects, are clearly influenced by the administration of leptin. Moreover, Applicants note that their chimeric form of the protein is superior to the native form of leptin, and thus, provides for an even greater advantage.

Moreover, the above references do not cast significant doubt on the currently claimed method (*e.g.*, Bell only notes that "there was considerable variability," rather than stating it did not work). While the above references are only tangentially relevant to the assertion of whether leptin will work (as they are general review articles and refer to particular forms or methods of use), Applicants note that not only their data, but also extrinsic references have clearly demonstrated that leptin works on normal (non-ob/ob mutants) animals. For example, Rosenbaum et al. (*J. Clin. Endro. & Metab.*, 87::2391-2394, 2002) notes that not only does leptin reduce weight loss in leptin-deficient rodents and humans, but it can also reduce weight in "leptin-sufficient animals and humans..." (p. 2391, second full paragraph). Applicants note that the amount of leptin required to achieve this is approximately 10 fold the normal amount, for normal leptin (of course, it should be less for the Applicant's chimeric leptin, as described below). There are additional references which demonstrate that leptin, when given in sufficient levels, does induce weight loss in leptin-sufficient animals. (*See also*, Campfield et al. 1995, *Sci.*, 269:546-48; Campfield et al., Sci. 280:1383-1387 (1998)("[i]t also causes reduction of food intake and body weight when administered to lean mice, rats, and monkeys" citing Campfield et al., *Horm. Metab. Res.*, 28:619; *Endocrinol. Metab.*, 4:81, 1997)). Thus, while the amount of OB protein required to induce the recited effects can be larger for some non-ob/ob animals, it is clear that, when given an appropriate, or "therapeutically effective amount," that the desired results will occur. We note that this is shown in Heymsfield et al. (Recombinant Leptin for Weight Loss in Obese and Lean Adults, JAMA, 282:1568-1575 (1999)), a copy of which is enclosed). What is apparent is that the references cited by the PTO are likely not tohave administered a therapeutically effective amount of the compound.

Additionally, Applicants note that the mere fact that something is leptin-resistant does not mean that they are leptin nonresponsive. Leptin resistance merely implies that increases in leptin do not result in as large a response as might otherwise be expected. Thus, administration of leptin to leptin-resistant individuals will simply require additional leptin to see the desired result. Applicants note the idea of "resistance" in science is common and does not typically denote absolute immunity. For example, type II diabetics are insulin-resistant, however, treatment of these individuals still involves insulin and actually involves administration of more insulin than would be given to an individual who is not insulin-resistant. Thus, "resistance" does not denote that leptin cannot work; it merely suggests that additional amounts of leptin (or more potent forms of leptin) are required to achieve the desired result.

Applicants respectfully remind the Examiner that "[o]ffice personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials. There is no decisional law that requires an applicant to provide data from human clinical trials to establish utility for an invention related to treatment of human disorders (see *In re Isaacs*, 347 F.2d 889, 146 U.S.P.Q. 193 (C.C.P.A. 1963); *In re Langer*, 503 F.2d 1380, 183 U.S.P.Q. 288 (C.C.P.A. 1974))" (M.P.E.P. § 2107.03). As noted above, there is current data on mice, monkeys, and humans, which demonstrate that the claimed method does work. This is more than sufficient to meet the standard for patentability.

Regarding the ability of chimeric leptin to treat bulimia, Applicants note that, as demonstrated by the present application, the level of leptin in bulimic patients is not, *per se*, relevant to whether or not leptin can be used to impact or alter a patient's characteristics. As noted above, when leptin is administered to mice with normal leptin levels, it still produces the desired results in those mice, even if their leptin levels are "normal." In light of these results, the fact that leptin levels could be "normal" in some bulimic patients is irrelevant, as leptin clearly has the desired impact, even in non-ob/ob animals, where there is, presumably, a normal amount of leptin. Additionally, as noted below, there are many references, published since the filing date of the current application, which continue to establish relationships between bulimia and leptin. The abstracts of these references are being submitted herewith.. As such, Applicants submit that the references cited by the PTO in the previous Office Action are not directly relevant to the

claimed invention, and that the present application and the references submitted herewith demonstrate the Examiner's requested connection between bulimia and leptin.

As per the request in the interview, Applicants are submitting numerous references to further verify a recognized association between bulimia and leptin. For example, Jimerson et al. (*J. Clin. Endo. & Metab.*, 85:4511-4514, 2000), entitled "Decreased Serum Leptin in Bulimia Nervosa," specifically notes that the results are consistent with the idea that, "decreased leptin function may be associated with alterations in eating patterns..." (abstract). Relationships are further described in "Impact of Binge Eating on Metabolic and Leptin Dynamics in Normal Young Women" (Taylor et al., *J. Clin. Endo. & Metab.* 1999) and in "Reduced Plasma Leptin Concentrations in Bulimia Nervosa," (Brewerton et al., *Psychoneuroendocrinology*, 25:649-658 (2000)).

Applicants note that any previous showing that leptin levels remained constant in patients suffering from the disorders merely emphasizes the novelty and nonobviousness of the claims. Moreover, Applicants submit that the above amendments to the claims are believed to have resolved these issues as well. Finally, in light of the fact that even ordinary leptin can induce a visible result in OB "normal" subjects, Applicants submit that a *prima facie* case of lack of adequate enablement has not been made. In particular, Applicants note that no reason for why the claimed method would not work in a manner commensurate with the claims has been provided. As noted herein, a "normal" level of OB protein in a subject does not mean that administering OB protein will not work on the subject. In light of the above, the applicants request that the rejection be withdrawn and Claims 24, 29, and 30 be allowed. Applicants note that new Claims 31-36 depend from Claim 24 and are also adequately enabled.

Rejection under 35 U.S.C. §102(e)

Claims 24, 29, and 30 stand rejected under 35 U.S.C. §102(e) as being anticipated by Pellymounter, U.S. Patent Application Publication No. 2003/0203837, filed 5/30/2003 and claiming priority to 11/22/1995.

Claims 24, 29, and 30 have been amended. The present claims recite that the condition to be treated is bulimia. Pellymounter does not describe the treatment of bulimia. Because each of the elements in the claims has not been taught by the cited reference, Applicants request that the rejection be withdrawn and the claims allowed.

Additionally, Applicants note that, in general, they do not concede the points asserted in the Office Action and reserve the right to make further distinctions as appropriate. For example, the phrase "therapeutically effective amount" is to be interpreted in light of the claims and the specification, from the view of one of skill in the art. Furthermore, the "effective amount" refers to the condition being treated. Thus, these can provide relevant limitations to the scope of the claims. Finally, while it has been asserted that "Pellymounter teaches a method with these limitations [*i.e.*, those in Claims 29 and 30], and therefore clearly anticipates Claims 29 and 30" (page 10, first paragraph), the rejection itself does not actually indicate where or how Pellymounter teaches the limitations of Claims 29 and 30. Applicants request that, if the rejection is to be maintained, that the specific teachings in the cited art of the elements in Claims 29 and 30 be set forth in the next Office Action.

In light of the above, Applicants request that the rejection of Claims 24, 25, 29, and 30 be withdrawn and the claims allowed. Applicants note that new Claims 31-36 depend from Claim 24, and as such, are also novel over Pellymounter.

Rejections under 35 U.S.C. §103(a)

Claims 14, 16-23, 26, and 28 stand rejected under 35 U.S.C. §103 as being obvious over Pellymounter in view of Capon et al (U.S. Pat. No. 5,455,165). As noted above, only Claims 24, 29, and 30 of the previously rejected claims are pending. These claims have not been rejected under 35 U.S.C. §103 (a). Applicants note that neither of the cited references addresses the treatment of bulimia. As all of the elements have not been taught by the combination of the references, a *prima facie* case of obviousness has not been established. As such, Applicants request that the rejection be withdrawn and the claims allowed.

Additionally, Applicants note that Capon's publication date is October 3, 1995. Applicants note that both Capon, and the present application, were assigned to Genentech Inc.

Applicants note that new Claims 31-36 depend from Claim 24, and as such, are also nonobvious over the cited art.

Rejections under 35 U.S.C. §103(a)

Claims 14, 16-26, and 28-30 stand rejected under 35 U.S.C. §103(a) as being unpatentable over any one of Zhang et al. (hereinafter "Zhang"), Basinski et al. ('744 or '886,

(hereinafter "Basinski")), DiMarchi et al ('954 or '336, hereinafter "DiMarchi"), in view of Shin et al. (hereinafter "Shin") or Ashkenazi et al. (hereinafter "Ashkenazi"). The Examiner has asserted that one of skill in the art would 1) not have thought that leptin acted on the brain and 2) not have thought that the blood-brain barrier was a relevant problem when considering the administration of a modified leptin protein.

As noted above, only Claims 24, 29, and 30-36 are pending. These claims recite a treatment for bulimia. The cited references do not teach the claimed method for the treatment of bulimia. The claimed method is for the treatment of bulimia in a patient having the disease; the method involves both the administration of the chimeric polypeptide to the particular patient, and the administration of an effective amount of the chimeric polypeptide. As these elements are not taught in the cited references, a *prima facie* case of obviousness has not been established. As such, Applicants request that the rejection be withdrawn and the claims allowed. Applicants note that new Claims 31-36 depend from Claim 24, and as such, are also nonobvious over the above cited combination.

Conclusion

Applicants respectfully submit that for the above recited reasons the current rejections should be withdrawn and that the present application is in condition for allowance. If, however, some issue remains, the Examiner is cordially invited to telephone the undersigned in order to resolve such issue promptly. Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 11/22/05

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